

Synthetic Penicillin

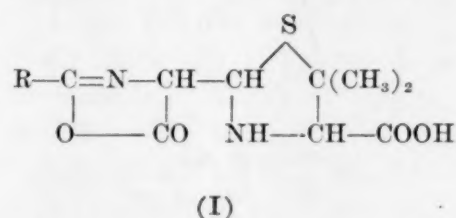
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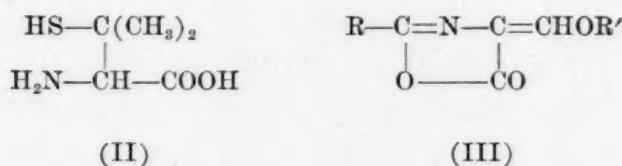
THIS REPORT IS A SUMMARY of the investigations that have led to the synthesis and isolation of G-penicillin (now termed *benzylpenicillin*). Most of the preliminary work, which is briefly described here, was performed by American and British chemists working under the joint auspices of the Committee on Medical Research, OSRD (Washington) and the Medical Research Council (London) (cf. *Science*, 1945, **102**, 627). The details of this preliminary work will be published in a monograph on penicillin chemistry, now in preparation.

The isolation in crystalline form of the active synthetic product and the unequivocal proof of its identity with natural benzylpenicillin have been carried out in this Laboratory since the termination of the OSRD contracts. Complete details of this latter work will be reported following the publication of the monograph.

In the early stages of the investigation of the chemistry of penicillin, the oxazolone-thiazolidine structure (I) was favored by the majority of laboratories



as representing the structure of penicillin. Consequently, much effort was directed toward the synthesis of compounds of Type I. An approach toward the synthesis of such compounds, which involved the condensation of an appropriate oxazolone, possessing a free or potential aldehyde group, with *d*-penicillamine (II) (1), was explored by several laboratories both in this country and in England. Oxazolones of Type III which possessed a potential aldehyde group were soon synthesized (2).



The formation, in such reactions, of products possessing antibiotic activity was demonstrated independently and almost simultaneously in the United States and in England and announced to the collaborating groups in the first months of 1944. The earliest record of this discovery is contained in a report from the laboratories of Merck and Company, Inc. (3), in which it was stated that "d(+)-penicillamine hydrochloride and the azlactone [(2-benzyl-4-methoxymethylene-5(4)-oxazolone) (III, R = C₆H₅CH₂-; R' = CH₃-)] have been reacted to give a product showing

This article was submitted for publication at the request of and through the Editorial Board of the monograph on the Chemistry of Penicillin being prepared under the auspices of the National Academy of Sciences.

The nomenclature used by the authors conforms with that to be employed in the forthcoming monograph on the Chemistry of Penicillin. According to this nomenclature G-penicillin is designated *benzylpenicillin*; K-, F-, and X-penicillins are designated, respectively, *n-heptylpenicillin*, Δ^2 -*pentenylpenicillin*, and *p-hydroxybenzylpenicillin*. This style of nomenclature is carried over into the naming of various degradation and rearrangement products of the penicillins. For example, G-penicilloic acid is designated *benzylpenicilloic acid*.

0.5 unit/mg. *in vitro* biological activity by the standard assay for penicillin G. This low order of activity has been obtained repeatedly, and is believed to be real. The active substance has properties similar to that of penicillin G." Shortly thereafter, the production of a similarly small amount of antibiotic activity from the condensation in cold glacial acetic acid containing sodium acetate, of 2-styryl-4-ethoxymethylene-5(4)-oxazolone with *dl*-penicillamine was described in detail by the Oxford group (4). It was later noted that in experiments where *l*- instead of *d*-penicillamine was used in the reaction no antibiotic activity was produced (5).

Although during the next year a considerable number of experiments by many laboratories were reported, in which the two compounds (*d*-penicillamine hydrochloride and 2-benzyl-4-methoxymethylene-5(4)-oxazolone) were allowed to react together under a variety of conditions, the best product that was obtained assayed only 3.6 units/mg. of material (the accepted value for sodium benzylpenicillin is 1,667 units/mg.). Because of the low order of activity of the material produced in this reaction, and also because it had become known that other compounds, not structurally related to penicillin, possessed detectable antibiotic activity when submitted to the routine assay methods, there was some doubt as to whether the activity produced in this reaction was due to the formation of a minute amount of penicillin or to the more extensive formation of substances of low intrinsic activity. During the next year further studies bearing on this point were reported.

In a study that was made of the relative stability of the antibiotic activity of the synthetic mixture and of benzylpenicillin, when treated with methanol, acid, or diazomethane, no difference in the gross rate of disappearance of the two activities was detected (6). A comparison was made of the relative antibiotic activities of the synthetic material and benzylpenicillin against seven bacteria. The two products gave the same relative responses (6).

This similarity of the synthetic material to benzylpenicillin in stability and "bacterial spectrum" offered strong evidence in support of the theory that penicillin was actually being synthesized in this reaction, but stronger evidence was soon obtained by the use of the isotope "tracer" technique (7). *dl*-Penicillamine containing radioactive sulfur was prepared and condensed with 2-benzyl-4-methoxymethylene-5(4)-oxazolone. Natural benzylpenicillin was added to the condensation product and isolated as the triethylammonium salt. This crystalline triethylammonium benzylpenicillin contained radioactive sulfur which was retained through a number of recrystallizations

and through conversion to two derivatives, namely, sodium benzylpenicillin and benzylpenicillic (G-penicillic) acid. Within experimental error the content of radioactive sulfur of the two derivatives remained constant.

Further evidence for the presence of penicillin in the synthetic reaction mixture was obtained through the use of the enzyme penicillinase (8). This enzyme, which rapidly inactivates penicillins, destroyed the antibiotic activity present in the synthetic reaction mixture.

The above evidence for the identity of the active material in the condensation reaction stimulated extensive investigations on the conditions of the reaction and also led to experiments designed to concentrate the antibiotic activity in the reaction mixture. Although no significant improvement in the yield of antibiotic activity in the synthetic reaction was obtained, some success in the concentration of the antibiotic activity was realized.

Partition chromatography of the condensation mixture over silica at pH 7 resulted in the ultimate isolation in The Upjohn Company laboratories of material with an activity of 44 units/mg. (9). A procedure of fractionation of the condensation mixture, based on the "counter-current distribution" principle (10), led to the preparation in our Laboratory of concentrates with activities of 30-50 units/mg., and in one instance a fraction with an activity of 275 units/mg. was isolated (11).

It was found that concentrates of 30-50 units/mg., when examined in the infrared region, showed an absorption band at 5.63μ .¹ This is the region of a characteristic absorption band in penicillin. A comparison was made of the *in vivo* excretion of concentrates of the synthetic activity and natural benzylpenicillin in rabbits. It was found that the ratio of excreted activity to that administered was the same within experimental error (11). Furthermore, the distribution coefficients for the synthetic and natural products were found to be the same in five different solvent pairs (11).

This overwhelming accumulation of evidence toward identity of the synthetic activity with benzylpenicillin warranted the conclusion that the condensation of *d*-penicillamine hydrochloride and 2-benzyl-4-methoxymethylene-5(4)-oxazolone represented a synthesis of benzylpenicillin, albeit in minute yield (11). Nevertheless, it was recognized that the only unequivocal confirmation of this conclusion lay in the actual isolation of the crystalline synthetic benzylpenicillin from the reaction mixture. This has now been

¹ The infrared measurements, carried out in the Physics Department of the University of Michigan, were performed on materials prepared in both the Upjohn and Cornell laboratories.

obtained through recent investigations in this Laboratory, which have culminated in the isolation of benzylpenicillin from the reaction mixture as the crystalline triethylammonium salt (12).

In the synthesis of benzylpenicillin for the isolation experiments a new procedure, which arose from studies on the mechanism of the synthetic reaction, was used. It had been found that when equimolar quantities of penicillamine hydrochloride and 2-benzyl-4-methoxymethylene-5(4)-oxazolone were condensed in pyridine containing triethylamine, a product was formed which was apparently free of starting material but possessed no antibiotic activity. When this product was then heated in pyridine containing pyridinium chloride, antibiotic activity was produced. These findings were utilized in modifying the original procedure. In the first step the *d*-penicillamine hydrochloride and the oxazolone were condensed to give a biologically inactive intermediate product, to be described later, which in the second step was activated by heating in pyridine containing pyridinium chloride. By this method a readily reproducible yield of activity was obtained in the synthesis, and the product so obtained appeared much more amenable to fractionation in our hands than products obtained by the one-stage synthesis.

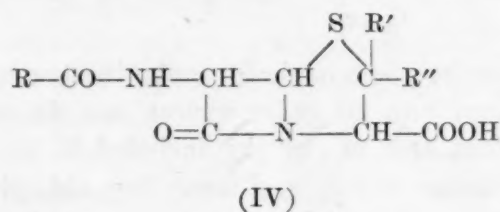
The above synthesis resulted in a reaction mixture which contained activity equivalent to about 0.1 per cent benzylpenicillin. The difficulty of isolation of the penicillin from the reaction mixture was enhanced by its innate instability. The method of fractionation that met with success in this particular case was based on the "counter-current distribution" principle (10). However, the isolation of the crystalline triethylammonium salt in amounts large enough for full characterization was realized only after careful standardization of each step of the procedure.

A preliminary concentration of the active material was effected by extraction of the penicillin from chloroform into 1.31 M phosphate buffer at pH 5.2. This was followed by an 8-plate "counter-current distribution" of the active material between ether and 2 M phosphate buffer at pH 4.88. The material obtained from the most active fractions of the 8-plate distribution was dissolved in chloroform, and a further concentration was obtained by extraction of the penicillin with 2 M phosphate buffer (pH 4.88). Finally, the last material was subjected to a 25-plate "counter-current distribution" between chloroform and 2 M phosphate buffer at pH 4.88. Crystals of the crude triethylammonium benzylpenicillin were prepared from the most active fractions of the 25-plate distribution. The salt was purified by crystallization from methylene dichloride by the addition of ether and finally recrystallized from acetone.

The melting point, ultraviolet and infrared absorption spectra, refractive indices, antibiotic activity, and specific rotation of the isolated triethylammonium salt of the synthetic material agreed, within the limits of experimental error, with the triethylammonium salt of natural benzylpenicillin. It is particularly noteworthy that the material isolated from this reaction mixture was the same optical isomer as the natural penicillin.

The isolation of benzylpenicillin from this reaction mixture proved conclusively that penicillin can be synthesized. Because of the obscurity of the reaction mechanism, the synthesis, at this stage of development, cannot be used as synthetic proof of structure of penicillin. However, as long as an unequivocal synthesis of penicillin by any other approach has not been demonstrated, the study of the mechanism of the above synthesis is extremely important. Such a study might lead either to a proof of structure or to an improved method of synthesis or both.

It should be pointed out that even at the present time it is possible to make, although in minute yields, new penicillins by the above reaction. The isolation of benzylpenicillin from the reaction of 2-benzyl-4-methoxymethylene-5(4)-oxazolone with *d*-penicillamine hydrochloride makes it clear that the antibiotic activity produced when oxazolones (13), substituted with other groups in the 2-position, were condensed with penicillamine was due to the synthesis of penicillins differing from benzylpenicillin in the nature of the group R, as illustrated on the basis of the β -lactam structure (IV). Moreover, the produc-



tion of antibiotic activity by the condensation of 2-benzyl-4-methoxymethylene-5(4)-oxazolone with various α -amino- β -mercapto acids other than *d*-penicillamine, such as *d*-cysteine, the thiolthreonines, and β -mercaptotoleucine (14), indicates the synthesis of analogues of penicillin differing from the known varieties of penicillin in the nature of the groups R' and R'' (IV). All the penicillins so far produced by the mold have contained *d*-penicillamine; the above observation opens the way to the synthesis, from other α -amino- β -mercapto acids, of a series of entirely new and different penicillins which might possess desirable therapeutic properties.

(See page 450 for list of references.)

Radar Observations During Meteor Showers

9 October 1946

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A SERIES OF RADAR OBSERVATIONS for the purpose of detecting ionization caused by meteors entering the earth's atmosphere was made by Central Radio Propagation Laboratory, National Bureau of Standards, at the suggestion of R. A. Helliwell, of Stanford University, beginning on 7 October 1946. An unusually rich meteor shower was expected on 9 October, during the passage of the earth through the orbit of the Giacobini-Zinner Comet. The observations were made at the Sterling, Virginia, Laboratory of the Bureau, where regular experiments in radio wave propagation are conducted.

The radar used for these observations was a standard Signal Corps type SCR-270-D, operating at about 107 megacycles, with its antenna oriented at an azimuth of 315° and with a vertical elevation angle of 45° . The width of the main beam of the radar antenna was approximately $40^\circ \times 20^\circ$ between half power points, the major axis being vertical. The radar transmitter had a peak pulse power of about 100 kilowatts. Visual observations, similar to those reported by Oliver Perry Ferrell in a letter to the editor of the *Physical Review* (1946, 69, 32), were made on the type A radar oscilloscope. Photographs were made of the observed echoes on a PPI presentation oscilloscope with a rotating time base having a period of two minutes; the antenna was, of course, not rotated. A sample photograph of the observed echoes is shown in Fig. 1.

Provision had been made for mounting two cameras synchronized with the radar camera in order to photograph that area of the sky included in the radar beam. Because of rain and heavy fog, this phase of the program could not be carried out. On 9 October the equipment was put in operation at 7:30 P.M., 75° W mean time. The "A" scope was monitored by an operator who kept a log showing the time, range, and approximate duration of all transient radar echoes observed. Fig. 2 shows data obtained by visual count of the echoes observed on the type A oscilloscope on the nights of 9 October and 11 October. The rate of occurrence rose from approximately 8 per hour between 7:30 and 8:30 to a peak of over 1 per minute between 10:30 and 11:30, which coincides approximately with the predicted time of 10:00 for the maximum intensity of the Draconid shower. Following this maximum the rate fell to about 20 per hour after 11:15. Distances ranged from about 60 miles to 200 miles. Duration of the transient radar reflections was

usually a second or less, although a considerable number lasted for several seconds. Only a few appeared to change distance during the time they could be observed on the screen, and these only in the order of five miles or less.

It is believed that most of the transient radar echoes observed during the tests were caused by meteors. Evidence leading to this belief is the range of distances over which the radar echoes were observed, the maximum rate of occurrence of the radar echoes on the night of 9 October at about the time predicted for the maximum intensity of the Draconid shower.

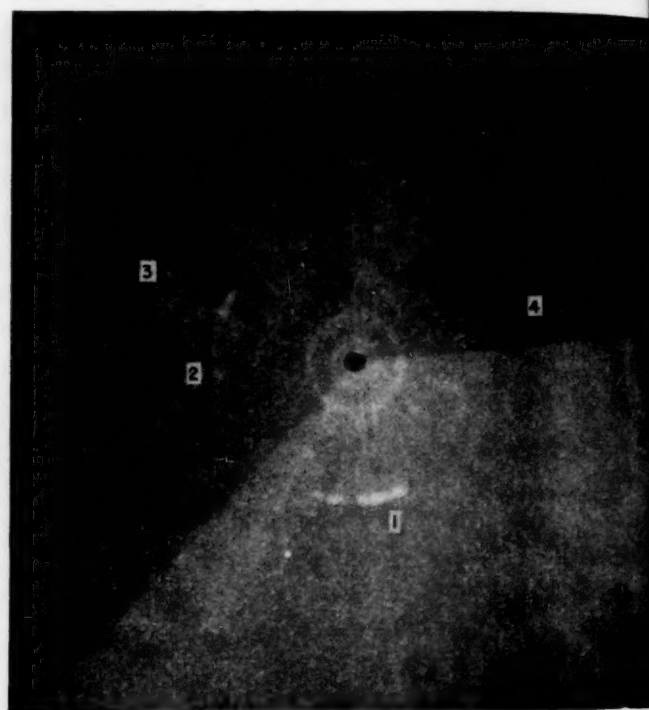


FIG. 1. Sample photograph taken of four transient radar echoes appearing on Radar PPI screen on night of 9 October 1946. Trace (1) indicates an approximate range of 75 miles and an echo duration of 15 seconds; (2) range, 75 miles; duration, 13 seconds; (3) range, 100 miles; duration $1/3$ second; (4) range, 85 miles; duration, $3/4$ seconds.

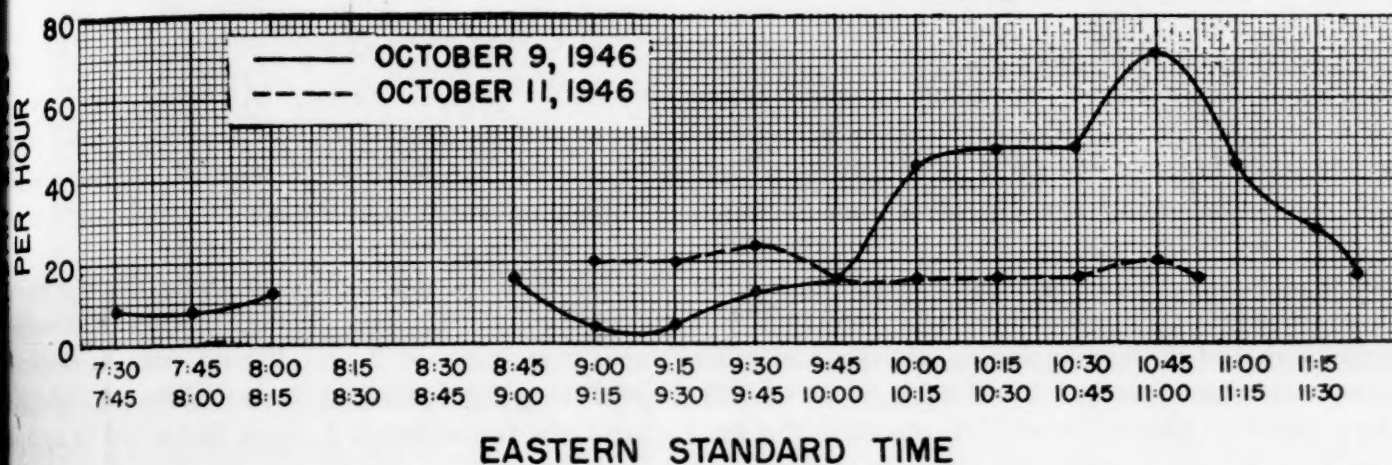
and the earlier observations of Ferrell and others of coincidences of radar echoes and visible meteors. Although no visible meteors could be observed on the nights of 7 to 9 October, because of clouds, visual and radar observations were made on the night of 10 October, in the course of which 7 visible meteors and 17 transient radar echoes were observed on the PPI oscilloscope. Preliminary analysis of the data taken indicates that in at least two cases the visual and radar observations were coincident in time. Further analysis of the PPI data may show additional coincidences. Rate of occurrences on other nights did not

hibit the marked peaking exhibited on 9 October, remaining at approximately the lower level of 9 October throughout the period of observation.

Since meteoric particles are of very small size, similar reflections directly from them may not be expected. The effects produced are undoubtedly from tracks of highly ionized atmospheric gases and meteoric vapors produced by the impact of the meteors in the atmosphere. Velocity relative to the earth of the meteoric particles from the Draconids is of the

vector parallel to the plane of the horizon, discrimination between vertical and horizontal tracks is to be expected. Reflections might not be obtained from visible tracks that are perpendicular to the plane of polarization, while some invisible tracks parallel to the plane of polarization might be detected by the radar. No unusual effects were noted on the regular ionospheric records obtained during the shower.

The encouraging nature of these preliminary results indicates that radar methods of observing meteors may



EASTERN STANDARD TIME

FIG. 2. Rate of occurrence of echoes on the nights of 9 and 11 October 1946 as observed with an Army type 270 Radar aimed 315° clockwise from North at an angle of 45° above the horizon (maximum hourly rate of occurrence of Draconids detected for night of 9 October).

er of 2×10^3 cm. per second. A meteoric particle having a mass of only 1 mg. might be expected to produce of the order of 10^{15} ions in passing through atmosphere if its entire kinetic energy is expended ionization. The reflections may thus be thought of due to scattering from a lengthy filament of highly ionizing atmosphere entirely different in nature from the layers which produce regular reflections of radio waves. Thus, since the radar employed for the observations emits a polarized beam with its electric

have a number of future applications. One such application would be the routine, continuous automatic recording of the radar echoes for determining the occurrence of meteors during overcast weather when seeing is poor and during daylight hours. It should also be possible to obtain much useful information regarding the nature and physical structure of the ionosphere with this type of radar equipment, as well as how meteor reflections may affect radio propagation and the usefulness of high frequencies.

The Department of Scientific and Industrial Research, London, reported to *Science* that the 9-10 October experiments on the radio method of detection of meteors, organized by Sir Edward Appleton and R. Naismith at the Slough Radio Research Station of DSIR, were completely successful. The report said that astronomers had predicted that the earth would enter the meteor stream of the comet, Giacobini-Zinner, at about midnight, but it was not until between 3:00 and 4:00 A.M. on the 10th that the stream had been entered.

The Radio Research Station first detected these echoes in 1932 and has continued to investigate them ever since. A theory was evolved that they were caused by the reflection of radio pulses from meteor trails, and evidence was progressively built up to support the theory. On this occasion the burst of echoes was on a scale greatly in excess of anything previously experienced. The methods used also permitted the average height of the meteor train to be determined, and this came out to be about 60 miles above the ground.

The report pointed out "that it was by purely scientific experiments of this kind that Sir Edward Appleton and the Radio Research Station developed the methods of detecting reflecting bodies at a distance, which later became the basis of practical radar."

Technical Papers

The Influence of Liver *L. casei* Factor on Spontaneous Breast Cancer in Mice¹

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In a previous publication (3) we reported that intravenous injections of crystalline *L. casei* factor led to complete regressions of spontaneous breast cancers in mice, in about one-third of the animals. We have been informed by Drs. Hutchings and Stokstad, of the Lederle Laboratories, that the correct tentative designation of this substance was fermentation *L. casei* factor. The isolation of this compound was announced, and its microbiological activity and other properties were described by Hutchings, *et al.* (2). More recently Angier, *et al.* (1) reported the syn-

Ninety-eight mice bearing single spontaneous breast cancers were selected for these studies. In each case a definite diagnosis of malignancy was established by biopsy. The animals were kept on a normal diet (Rockland mouse pellets). Three groups were formed. The first group, 39 tumor mice, received 5 µg. of liver *L. casei* factor; the second group, 31 mice, received 100 µg. of the liver *L. casei* factor; and the third group, 28 mice, received 5 µg. of the crystalline fermentation *L. casei* factor. All substances were injected intravenously daily for a period of 4-6 weeks. As control, the data of 71 mice of the same strain which were observed in the laboratory during a period prior to this experiment, were used.

The results are presented in Table 1. It is evident that the liver *L. casei* factor, administered intravenously in doses of 5 and 100 µg. was ineffective in producing regressions of these tumors. On the other hand, the fermentation *L. casei* factor led to complete

TABLE 1

Group	No. of mice	Substance and dose (µg.)	No. of mice with complete regressions of tumors	No. of mice with new tumors	No. of mice with lung metastases	Mean life span in days*	S.D.	Significance of difference
1	71	0	0	19	13 among 61	74 ± 6.2	51.9	Between Groups 1 and 3: 2.2
2	39	Liver <i>L. casei</i> factor (5 µg.)	1	12	19 among 32	75 ± 6	38.2	Between Groups 2 and 3: 2.4
3	31	Liver <i>L. casei</i> factor (100 µg.)	0	11	3 among 30	55 ± 6	33.5
4	28	Fermentation <i>L. casei</i> factor (5 µg.)	11	2	†	After 100 days 23 mice alive

* Life span calculated after start of experiment.

† An evaluation cannot be given since the majority of mice in this group are alive.

thesis of a compound identical with the *L. casei* factor from liver. This substance differs in microbiological activity from that of the fermentation *L. casei* factor used in our previously reported experiments in that the liver *L. casei* factor is about 17 times as active for the test organism, *Streptococcus lactis* R, at half maximum growth.

In the following communication we present evidence that the action of the liver *L. casei* factor is unlike that of the fermentation *L. casei* factor in therapeutic effect on spontaneous tumors in mice.

¹ This work was aided by the Philip J. Goodhart bequest. The liver *L. casei* factor was supplied by the courtesy of the Lederle Laboratories.

² The authors wish to acknowledge with deep appreciation the assistance of Miss Ellen Borenfreund and Miss Thea Neuringer in the experimental work.

regression of tumors in 11 of 28 mice, which is in agreement with previous observations made in our laboratory. It is interesting to note that while in the control group and the group treated with 5 µg. of the liver *L. casei* factor had the same approximate mean life span, there was a significant increase in the incidence of lung metastases in the latter group. In the group which received the 100-µg. dose of the liver *L. casei* factor, only 3 out of 30 mice showed lung metastases. This lowered incidence of lung metastases can best be understood by comparing the mean life span of this group with that of the group which received 5 µg. of the liver *L. casei* factor and with that of the control group. The mean life span of the group receiving the 100-µg. dose was reduced from

to 55 days, and therefore the mice evidently did not live long enough to develop the lung metastases. The 3 mice which did show metastases at death lived 90 days. It was apparent during the experiment that the primary tumors of the mice receiving the 100- μ g doses of liver *L. casei* factor intravenously were growing much more rapidly than the tumors of untreated controls. Unfortunately, the wide fluctuations in the growth rate of these tumors do not allow any quantitative evaluation.

Whether these findings apply only to the particular strain of mice and method of assay used in these experiments needs further investigation. No conclusions should be drawn from these animal experiments as to the action of the liver *L. casei* factor on human cancer.

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Stability of Carotene in Dehydrated Carrots Impregnated With Antioxidants¹

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Deterioration in quality of dehydrated carrots is usually associated with two different types of changes. One of these, resulting in a darkening of the carrots, occurs in an aqueous phase and is concerned with the union of amino acids and sugars—the so-called Maillard reaction. The other is made evident by the deterioration of the carotenoid pigment and is probably allied to the oxidative rancidity of the carrot oils. This report is concerned with the latter phase of deterioration.

We have shown in previous publications that, when carrots are dried, the carotene goes into solution in droplets of oil and that, upon storage, the carotene disappears, leaving colorless droplets which give a positive test for aldehydes with Schiff's reagent (3). It has been reported that carotene dissolved in oil hastens the oxidation of the oil (1). Furthermore, carotene is degraded concurrently with the oxidation of fats (2). These observations suggest that the oil droplets in the cells of dried carrots are undergoing oxidative changes and that the carotene is degraded as a result of these changes.

Blanching improves the stability of the carotenoids but does not stop their deterioration. Furthermore,

¹The subject matter of this paper has been undertaken in cooperation with the Quartermaster Corps Committee on Food Research.

leaching blanched carrots before storage accelerates the rate of pigment breakdown. (Compare Items 6, 7, and 8 with Item 15 in Table 1.) Tests with carrots which had been blanched but not dried showed that the rate of pigment breakdown could be retarded by the application of antioxidants (4). This paper reports the results of a survey of the action of some 30 tests of various antioxidants on blanched, dried carrots. The tests were carried out on carrots harvested during the summer.

Imperator carrots, about 4 months of age, were harvested during August, sliced (2–3 mm. thick), and blanched in steam for 5 minutes. The blanched slices were soaked for 5 minutes in solutions of various antioxidants. They were drained and dried in a tunnel dehydrator at approximately 60° C. to a moisture con-

TABLE 1

Treatment	Carotenoids remaining in samples after storage at 40° C. (%)				
	48 hr.	72 hr.	96 hr.	120 hr.	168 hr.
(1) .01% N.D.G.A.* + .3% Na ₂ S ₂ O ₅ (in 40% ethanol) . .		95.8			91.5
(2) .1% pyrogallol + .2% Na ₂ S ₂ O ₅ . .	94.5				91.3
(3) .1% ascorbic acid		101.0		93.0	89.5
(4) .1% pyrogallol . .		94.5			85.1
(5) .01% N.D.G.A. (in 40% ethanol) . .		98.7		85.5	82.0
(6) Blanch only		93.0		91.0	77.0
(7) " "	94.0		92.0		75.0
(8) " "	94.0		91.0		74.0
(9) .1% piperidine . .	94.0		89.0		76.0
(10) .2% pyrrole (in 40% ethanol) . .	95.0		89.0		75.0
(11) .1% hydroquinone	97.0				74.0
(12) .2% lecithin (in 40% ethanol) . .	94.0		87.0		71.0
(13) Blanch	83.0		76.0		67.0
(14) 40% ethanol leach	93.0		77.0		57.0
(15) Water leach	82.0		73.0		45.0

Other substances tested: hemin, tocopherol, tocopherol plus ascorbic acid, piperidine plus SO₂, phosphate buffer pH7, phosphate plus SO₂, diphenylamine, *p*-phenylene diamine dihydrochloride, N.D.G.A. plus ascorbic acid, gallic acid, maleic acid, oxalic acid, γ -tocopherol palmitate, and α -tocopherol succinate.

* N.D.G.A. = nordihydroguaiaretic acid.

tent of about 6 per cent and then ground on a Wiley mill to pass a 20-mesh screen, the smaller particles being sifted through a 48-mesh screen on a Rotap machine and discarded. The remaining grains were divided, half being stored in an incubator at 40° C., and half stored at room temperature. Both storage tests were carried out in darkness. Pigment concentration, in an acetone extract, was measured on the Evelyn colorimeter using the 440 filter.

The antioxidants tested are shown in Table 1. Since the procedure for impregnation of the antioxidants required a 5-minute soak in the solution of the antioxidant to be tested, standards for comparison were

prepared by soaking blanched carrots in distilled water or 40 per cent ethanol for 5 minutes (Items 14 and 15). Pigment breakdown was also followed in stored samples that had received no treatment other than blanching (Items 6, 7, 8). These latter experiments served as a general check on the series of tests.

A slower rate of pigment breakdown than that found for the water and ethanol-treated samples (Items 14 and 15) would indicate that the materials with which the carrots were impregnated were exercising some protective action. Practically, of course, any added substance must result in a slower rate of breakdown than that found after blanch only.

Those materials which protect the carotenoids in carrots stored at 40° C. are listed in the order of their potency in Table 1. Those compounds which do not retard the breakdown of the pigments are listed without inclusion of figures or placement in any order.

Item 13 may be of significance. The carrots of this test were blanched, dried, ground, and stored at 4° C. for about 8 weeks before being transferred to 40° C. for the regular storage test. No change in the pigment, measurable on the Evelyn colorimeter, occurred during cold storage. Rate of breakdown at 40° C., however, was much more rapid than that of samples stored at 40° C., immediately after preparation.

The erratic results for thiourea and sodium metabisulphite at 40° C. are not reported.

The samples held at room temperature were analyzed for pigment content after 2 and 4 months storage (Table 2). Since the samples were placed in storage during the fall, those stored early in September were subjected to higher temperatures than those stored at the end of the month. For this reason the table is divided into two parts.

We conclude that:

(1) The carotenoids in summer-harvested, blanched, dehydrated carrots may be stabilized by certain antioxidants.

(2) In general, those antioxidants which were effective at 40° C. were also effective at room temperature. The following exceptions may be noted: lecithin, in relation to the other substances, was not as effective at room temperature as at 40° C.; R (an antioxidant obtained from the Dairy Industry Division) and a combination of a phosphate buffer (pH 7.1) and .3 per cent $\text{Na}_2\text{S}_2\text{O}_5$, were, in relation to other substances, more effective at room temperature than at 40° C.

(3) The effectiveness of .1 per cent pyrogallol + .1 per cent $\text{Na}_2\text{S}_2\text{O}_5$ was markedly greater than that of any other substance or substances. Carrots treated with this mixture contained more of the original carotene content (79 per cent) after 4 months storage than other samples did after 2 months storage (Table

2). The combination is more effective than either substance alone. Color retention is good, and no unpleasant odor developed.

(4) There is a good correlation between odor and carotenoid degradation. Those samples with a high carotene content retained a pleasant smell. No tasting tests have as yet been tried.

TABLE 2

Antioxidant	Carotenoids remaining in samples after room storage (%)		Comparison with 40° C. storage as shown by relative rank in Table 1
	2 mos.	4 mos.	
A. Stored between 6 September and 17 January			
(1) .1% ascorbic acid and .08% tocopherols (in 40% ethanol)	54	37	Not tabulated but similar to ascorbic acid alone
(2) .1% ascorbic acid	57	34	3
(3) .01% N.D.G.A. (in 40% ethanol)	46	34	5
(4) .1% piperidine	43	31	9
(5) R	54	30	Poor, not tabulated
(6) .2% pyrrole (in 40% ethanol)	44	27	10
(7) .1% piperidine + .5% Na ₂ S ₂ O ₅	33	20	Poor, not tabulated
(8) 40% ethanol leach	20	12	14
(9) Water leach	18	8	15
(10) Blanch only	21	7	6
(11) .2% lecithin (in 40% ethanol)	20	1	12
(12) .07% tocopherols (in 40% ethanol)	27	1	Poor, not tabulated
(13) .01% hemin	6	1	" " "
B. Stored between 26 September and 26 January			
(1) .1% pyrogallol + .2% Na ₂ S ₂ O ₅	100	79	2
(2) .1% pyrogallol	69	55	4
(3) .01% N.D.G.A. + .3% Na ₂ S ₂ O ₅	71	53	1
(4) .1% hydroquinone	62	43	11
(5) Phosphate buffer pH 7.1 + .3% Na ₂ S ₂ O ₅	61	38	Poor, not tabulated
(6) .1% diphenylamine (in 40% ethanol)	37	33	" " "
(7) .5% Na ₂ S ₂ O ₅	58	23	" " "
(8) .1% p-phenylene diamine	26	17	" " "
(9) Phosphate buffer pH 7.1	18	11	" " "
(10) .1% gallic acid	7.1	7	" " "

In work on blanched, undried carrots it was found that the carotenoids were much more stable in winter than in summer. Similar results are being obtained with dried carrots. Pigment breakdown in winter-harvested carrots approximates that obtained for summer carrots treated with ascorbic acid. The protective action of ascorbic acid on the carotenoids in winter-harvested carrots is correspondingly lessened.

These results, which in no way refer to the suitability of these materials for use in foodstuffs, have been obtained from experiments on summer-harvested carrots. It is very possible that different results will be obtained from studies on winter-harvested material.

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Synthetic *L. casei* Factor (Folic Acid) in Treating Certain Anemias in Man^{1,2}

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Folic acid has been shown to be an important anti-anemic factor in chicks (2), rats (3), and monkeys (5). Spies, *et al.* (7, 9) have reported that synthetic folic acid has a striking antianemic effect in several types of macrocytic anemia in man. Darby, Jones, and Johnson (4) have administered synthetic *L. casei* factor to three patients with sprue and obtained marked improvement in clinical and hematologic findings. Moore, *et al.* (6) have shown *L. casei* factor to be effective in inducing remissions in pernicious anemia, sprue, and macrocytic anemia of pregnancy.

Synthetic *L. casei* factor (1) has been given as the sole therapeutic agent to five patients with severe anemia. One patient had typical pernicious anemia; three, nutritional macrocytic anemia; and one, normocytic anemia with hypoplastic bone marrow. The patients with nutritional macrocytic anemia had a dietary history which indicated deficiency of vitamins of the B complex, and two of them were found to have free hydrochloric acid in the gastric juice. In one patient the bone marrow was hypercellular with a predominance of megaloblasts; in the other two it was hypocellular, a few megaloblasts being present in one instance and a few normoblasts and pronormoblasts in the other. Extensive investigation in each of these patients failed to reveal any condition such as infection, neoplasm, or loss of blood, which might have contributed to the development of anemia.

L. casei factor was administered intramuscularly to four of the patients in amounts of 15 mg. daily for 19 or 20 days. Throughout the period of study the diet was low in protein and free of meat except in the patient having normocytic hypoplastic anemia, who received the regular hospital diet. A reticulocyte response occurred in each case beginning on the 2nd to the 6th day, reaching a maximum between the 5th and 9th days of treatment and continuing for 8 to 15 days. The maximum rise in reticulocytes varied from 5.4 to 9.8 per cent.

There was a rise in the erythrocyte count and in hemoglobin concentration within a week after therapy was instituted, this increase continuing until the 24th to 43rd day, when the maximum was attained. Hematologic findings in the several patients were as follows: before therapy: erythrocytes, 1.7–2.3 mil-

lion/mm.³; hemoglobin concentration, 4.9–7.0 grams per cent; hematocrit, 14–22 per cent of packed red blood cells; following therapy: erythrocytes, 3.4–4.5 million; hemoglobin, 9–12 grams per cent; hematocrit, 34–39.5 per cent of packed red blood cells. At the last observation, 7 to 9 weeks after beginning treatment, improvement had been essentially maintained. The bone marrow was re-examined 4 to 6 weeks after therapy with *L. casei* factor had been instituted and in each instance was approaching normal, regardless of whether the initial picture had been one of stimulation or depression of the erythroid series.

In two patients the initial leucocyte count was low. This rose to normal during therapy, and the percentage of granulocytes increased.

One patient who had nutritional macrocytic anemia has been under observation since April 1944 and has been treated with folic acid concentrate and with synthetic *L. casei* factor in varying amounts on six occasions (5–15 mg. daily for 7–10 days orally or intramuscularly). There was an increase in hemoglobin and in erythrocytes in each of the six tests. The maximum reticulocyte response to folic acid concentrate was 12 per cent; to synthetic *L. casei* factor, 8.8 per cent. In two instances there was no rise in the reticulocyte count, and yet hematologic improvement occurred. *L. casei* factor was effective when administered either orally or parenterally. In June 1944 this patient was given 195 units of concentrated liver extract intramuscularly during a period of one month. The erythrocyte count and hemoglobin concentration increased markedly, but normal levels were not attained. Oral liver extract, brewers' yeast, iron, and a combination of thiamine, riboflavin, and niacin had no effect on the blood picture.

In all of the patients to whom *L. casei* factor was administered there was an improvement in general physical condition concomitant with the improvement in hematologic status. From these data and those previously reported by others *L. casei* factor appears to be a potent antianemic principle for man. The activity of this factor closely resembles, but is apparently not identical with, that of the antipernicious anemia principle in liver.

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² Synthetic *L. casei* factor was furnished through the courtesy of Drs. W. H. Sebrell and F. S. Daft, of the National Institute of Health, and Dr. Stanton M. Hardy, of Lederle Laboratories.

News and Notes

About People

H. J. Muller, geneticist, and professor of zoology at the University of Indiana, was awarded the Nobel Prize in medicine and physiology for 1946 on 31 October.

The work which won the award had come to the attention of AAAS in 1927 when Dr. Muller was cited for his paper, "The influence of X-rays on genes and chromosomes."

At that time Dr. Muller won the \$1,000 prize for "a paper of high importance" awarded by the AAAS annually through an anonymous donor.

News of the Nobel award reached Dr. Muller in Washington where he was attending a three-day conference at the Carnegie Institution.

As a graduate student, Dr. Muller worked with Thomas Hunt Morgan at Columbia University between 1912 and 1915. Dr. Morgan's work in genetics won the Nobel Prize in 1933.

At present Dr. Muller is engaged in a new research program at Indiana University which has the support of the Rockefeller Foundation and the Cancer Research Institute.

Herbert E. Wright, Jr., professor of geology, Brown University, and two of his students who spent the summer in New Mexico making a geological map of the Chuska Mountains have returned to Brown with their findings. Although in 1915 a government expedition made a general survey of the Navajo Desert area, including the Chuska Mountains, Dr. Wright is the first to make a detailed study of special features of the mountains. Dr. Wright, accompanied by Joseph A. Birman, Seekonk, Massachusetts, and H. T. Ames, Wellesley, Massachusetts, went to study the area, known as the Defiance Monocline, on a project grant from the Geological Society of America.

George W. Rawson, formerly in charge of the Section of Parasitology, Research Department of Parke, Davis and Company, Detroit, is now in charge of Veterinary Clinical Research, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Elmer H. Stotz, head of the Division of Food Science and Technology at the New York State Agricultural Experiment Station, Geneva, has been appointed professor of biochemistry and chairman of the Department of Biochemistry, University of Rochester School of Medicine and Dentistry. Dr. Stotz will succeed Walter R. Bloor, professor of biochemistry and pharmacology and associate dean of the School

of Medicine, when the latter retires from the faculty next June. Dr. Bloor has been a professor at the Medical School since 1922.

Fenner A. Chace, Jr., formerly curator of Crustacea at the Museum of Comparative Zoology, Harvard University, was appointed curator of Marine Invertebrates at the U. S. National Museum on 1 August. His associate curator is Arthur G. Humes, until recently assistant professor of biology, University of Buffalo, who was appointed to the Museum staff on 1 October.

Frederick M. Swain has been appointed assistant professor in the Department of Geology and Mineralogy, University of Minnesota. Dr. Swain, formerly at Pennsylvania State College and earlier with Phillips Petroleum Company, the U. S. Geological Survey, and the Pennsylvania Railroad System, will teach petroleum geology and micropaleontology.

R. M. Brucer, formerly lieutenant colonel in the Medical Corps of the Airborne Troop Service, has been appointed instructor in the Department of Physiology, University of Texas Medical Branch, Galveston. Dr. Brucer will carry forward research work associated with aviation physiology.

Ray L. Watterson, formerly of the University of California, has been appointed assistant professor of zoology at the University of Chicago.

Richard L. Laubengayer was recently made assistant professor of botany at Wabash College, Crawfordsville, Indiana.

Allen O. Whipple, former professor of surgery, College of Physicians and Surgeons, Columbia University, and winner of the Katherine Berkan Judd Prize, awarded each year to the person making the greatest advancement toward the discovery of a cure for cancer, has been appointed clinical director of Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York. Before taking up his new duties on 1 February 1947 Dr. Whipple will go to England to study the cancer program in that country. He will also visit the University of Beirut, of which he is a trustee, and act as consultant in the reorganization of its Medical School. Dr. Whipple will head the expanded teaching program to which the Memorial Cancer Center committed itself during its recent campaign to raise \$8,000,000. The addition of 100 beds to the present hospital, the 300-bed Ewing Hospital to be built by the City of New York, and the Sloan-Kettering Institute for Cancer Research, made pos-

sible by a gift of \$4,000,000 from Alfred P. Sloan, Jr., will make Memorial the most complete cancer center in the world.

Announcements

Only one scientist was appointed to the new Atomic Energy Commission, as announced by President Truman on 28 October. He is Robert F. Bacher. Dr. Bacher, who is now professor of physics at Cornell University, actually assembled the vital core of the first atomic bomb on 12 July 1945. He has, of recent weeks, been in New York City as technical adviser to Bernard M. Baruch, the American representative on the UN Atomic Energy Commission. The chairman of the five-man Commission named by the President is David E. Lilienthal, who resigned as chairman of the Tennessee Valley Authority to accept the new appointment and who is co-author of the Lilienthal-Acheson report issued by the State Department dealing with control of atomic energy (*Science*, 1946, **103**, 428, 451). In addition to Dr. Bacher, to serve with Lilienthal the President appointed: Lewis L. Strauss, a partner of the banking firm of Kuhn, Loeb & Company, who served in the Navy during the war; Sumner T. Pike, a former member of the Securities and Exchange Commission and a former director of the Fuel Division of OPA; and William Waymack, of the *Des Moines Register and Tribune*. Mr. Waymack is a Pulitzer laureate in editorial writing.

The President also appointed Gordon Rufus Clapp, who has been general manager of TVA, as successor to Lilienthal for the remainder of his term, which will expire in May 1954. All of these appointments are subject to confirmation by the Senate when it meets in January, but the appointments are to start immediately on a provisional basis.

Following this announcement, the Associated Press issued a concise summary of the provisions of the Lilienthal-Acheson report charging the new commission with these responsibilities:

Conduct its own research, and promote research by others.

Own and operate facilities for making fissionable material. No one else may do this except under license from the commission.

Own all plutonium, uranium, and other material which the commission deems capable of releasing "substantial quantities" of atomic energy. Any now privately owned will be taken over and paid for.

Prospect for new material.

Buy fissionable material abroad, if necessary for defense.

Distribute atomic material for research of medical use, making its own rules as to charges and other terms.

Conduct military research and make atom bombs for the armed forces.

License the manufacture of equipment and devices for using atomic energy.

Issue reports on any atomic energy developments for industrial and commercial use.

Take over for public use, with just compensation, any patents for making or using atomic energy.

Control any dissemination of secret information.

Issue regulations for safety, health, and other purposes in the atomic field.

Report to Congress at least twice a year.

An exhibit of books, prints, and manuscripts on the development of anesthesia, to commemorate with the Army Medical Library the 100th anniversary of the first public demonstration of ether anesthesia, opened in the Library of Congress on 16 October. The exhibit will remain on view until 30 November on the main floor of the North Gallery of the Library.

Ether was first used publicly as an anesthetic on 16 October 1846 by William T. G. Morton, a dentist who put a young man to sleep in the operating amphitheater of the Massachusetts General Hospital while John C. Warren, surgeon, removed a tumor from the patient's neck. The discovery, however, was made almost simultaneously by several persons, and the conflicting claims made for credit and priority constitute one of the most acrimonious quarrels in medical history.

The exhibit in the Library of Congress illustrates the growth of man's knowledge of anesthesia from preanesthetic days until modern times. Among the rarities shown is a dissertation, published at Rostock in 1718, which contains one of the earliest known uses of the term anesthesia. The dissertation is from the collections of the Army Medical Library. Other notable items include papers from the Crawford W. Long Collection in the Library of Congress and one of the rare *Letheon* tracts by Dr. Morton, explaining the use of his new anesthetic.

"Freezing Projects in Progress—1946," a report issued by the Frozen Food Foundation, Inc., Syracuse, New York, details the work of almost 350 research projects being carried on by business groups, government agencies, and universities. The listing of projects indicates that research is about evenly divided between adaptability of various foods to freezing and problems of processing, packaging, storage, and use. The publication is designed to serve as a clearing-house for research activities in the frozen food field, and lists not only the organizations and projects but also the names of individual research workers. A non-profit research and service organization, the Foundation was established early in 1945 for leading U. S. and Canadian department stores and industrial companies interested in frozen foods.

A grant in honor of *Federigo Enriques*, mathematician and science historian who died in Rome on 14 June, is being established by a group of his students in order to assist some of his pupils in the continuance of their scientific careers. The Committee is requesting all those who knew Prof. Enriques or his writings to take part in the commemoration, whether or not a financial gift is included. The acceptance may be sent to: Casa Editrice Zanichelli, Bologna, Italy. The choice of pupils to be helped and the partition of the grant will be made by Guido Castelnuovo, Oscar Chisini, Luigi Campedelli, Giovanni Enriques, and Ezio della Monica, director of the Publishing House Zanichelli.

The *encyclopedia of chemical reactions* was previously discussed in *Science* (1934, 79, 541) and has been publicized several times in different journals since that time. In view of the fact that the first volume of this work is now in print, many people have inquired how soon they may expect the remaining volumes and how many there will be. It is hoped that Volume II will appear early next year, for the assembling of the reactions constituting this volume began about 1 October. There will be at least four additional volumes, according to the editor-in-chief, C. A. Jacobson.

More than 60 abstractors submitted reactions for Volume I, and 15 collaborators assisted in the editorial work. The 3,076 chemical reactions contained in Volume I are listed alphabetically with respect to both the reactants and the substances produced in the reactions. Each reaction contains a descriptive paragraph setting forth the conditions governing the reaction, such as temperature, solvent, current density, etc. The reaction is finally epitomized by an equation of chemical formulas giving the starting materials and the products formed. Below this will be found the name of the author, together with the place of publication. Each abstractor is given a number, which appears after every reaction submitted by him. Besides a complete list of the journals used by the abstractors there are two exhaustive indexes, one for the reagents and one for the substances formed.

Volume I deals with the reactions under aluminum, antimony, arsenic, barium, beryllium, bismuth, boron, and bromine. Volume II will include reactions under the elements beginning with the letter C.

There are still some chemical journals that have not been abstracted and several that have been started but not completed. In order to make the encyclopedia complete and exhaustive it is essential to secure more abstractors who are willing to donate some of their spare time to the project. Abstractors will receive a small share of the royalty, a free copy of the encyclo-

pedia, and permanent recognition in this "monumental work." Those interested in obtaining abstracting assignments should communicate with Dr. Jacobson, whose address is P.O. Box 123, Morgantown, West Virginia.

The *New York Academy of Medicine*, through its president, George Baehr, announced on 14 October that it has provided facilities for the World Health Organization of the United Nations in its building until such time as the Organization has a permanent home. Although the secretariat of UN will be located in the United States, no decision has been reached as yet concerning whether the World Health Organization will find its permanent home in the buildings of the former Health Section of the League of Nations, or whether it will be located in some other large European city or in this country. Because of the difficulty of finding space in New York City for a temporary period, the Organization appealed to the Academy and, by rearrangement of other activities within the Academy building, space has been provided in which the Interim Commission can carry on its activities. The Organization was established by the International Health Conference, convened by the Economic and Social Council of UN, which met in New York from 19 June to 22 July 1946 (see *Science*, 1946, 104, 281-283).

W. A. Collier, protozoologist and bacteriologist, who was a prisoner of war of the Japanese and is at present in charge of the Rabies and Smallpox Division, Institute Pasteur, Bandoeng, Netherlands East Indies, has asked urgently for reprints in the field of bacteriology and experimental medicine and particularly for volumes of the *American Review of Tuberculosis* covering the period 1944-46.

The *Charles C. Adams collection of Odonata*, including about 3,900 insects, representing 337 species, has been presented to the Academy of Natural Sciences of Philadelphia. Dr. Adams personally collected most of the insects native to Illinois and the upper waters of the Cumberland and Tennessee Rivers. Other localities of origin and collectors include: Gotha, Florida (Adolph Hempel); Phoenix, Arizona (R. E. Kunze); Intervale, New Hampshire (G. M. Allen); Orono, Maine (F. L. Harvey); the Nilgiris, India (a native collector); and European localities (René Martin). Many examples from Dr. Adams' collection are recorded in the Odonata section of the *Biologia Centrali-Americana*. Dr. Adams made the presentation in recognition of the contribution made to the knowledge of Odonata by Philip P. Calvert, a research fellow in entomology at the Academy for many years.

Meanwhile, a bottomless cup descends upon the section, and a few drops of hot chemical solutions are sprayed in sequence onto the exposed film, which is then cleared by vacuum. Because of the high temperature, 140° F., processing is completed in about 9 seconds. The nearly dry photographic image, a direct positive picture, is then pulled to the projection system, where air pressure completes the drying, cools the film, and holds it flat during immediate projection on the screen and convenient examination by an audience. The complete cycle from exposure to projection is repeated every 15 seconds and provides a permanent record.

Development of processing of this type is part of a larger program of research on rapid processing being carried out in Kodak Research Laboratories for the television field, documentary reproduction, and the rapid recording of scientific data, such as the traces on oscillograph screens.

The National Academy of Sciences, at its recent meeting, awarded the Alexander Agassiz Medal to Joseph Proudman, F.R.S., director of the Liverpool Observatory and Tidal Institute. Since Prof. Proudman was unable to be present in person, the medal was accepted in his behalf by Sir Alfred Egerton, secretary of the Royal Society, London.

The Daniel Giraud Elliot Medal went to George Gaylord Simpson, paleontologist, the American Museum of Natural History. The Mary Clark Thompson Medal was presented to John B. Reeside, Jr., of the U. S. Geological Survey.

The Howe Lecture of Ophthalmology will be given by William John Brownlow Riddell, fellow of the Royal Faculty of Physicians and Surgeons and dean of Medicine at Glasgow University, at the Harvard Medical School on Tuesday, 19 November. The title is to be "Heredity and Variation in Clinical Ophthalmology."

Meetings

The 28th Annual National Metal Congress will meet at Atlantic City on 18 November, under the sponsorship of the American Society for Metals. Participating societies are: American Welding Society; Iron and Steel Division and Institute of Metals Division of the American Institute of Mining and Metallurgical Engineers; and American Industrial Radium and X-Ray Society. Sixty-four technical papers will be presented.

Several special lectures which will be given during the week include: the Campbell Memorial Lecture, by J. B. Austin, of the U. S. Steel Corporation; the annual banquet lecture, by Walter S. Towers, president of the American Iron and Steel Institute; the Adams Lecture, by W. F. Hess, of Rensselaer Polytechnic In-

stitute; an address before the A.I.M.E. by W. Hume-Rothery, of Oxford; and the retiring address by Kent R. Van Horn, president of the American Industrial Radium and X-Ray Society.

The National Metal Exposition, also sponsored by A.S.M., will include product and methods displays from over 400 companies, covering every phase of the metal industries. A special feature of the Exposition will be an exhibit of photomicrographs. Prizes will be given for the print judged best in each classification. The Exposition will be held in the Municipal Auditorium; admission is free to all members of technical societies and to those holding invitations distributed by participating firms.

Recent Deaths

LeRoy Samuel Weatherby, 66, professor of Chemistry, University of Southern California, died on 10 October at his home in Los Angeles.

Carlos G. Williams, 83, director emeritus of the Ohio Agricultural Experiment Station, died on 4 October in Wooster, Ohio. Dr. Williams was best known as a plant breeder of cereals and as a contributor to the farm press on agronomic subjects.

Ignace Moscicki, 78, president of Poland from 1918 until the start of World War II, and one of Europe's greatest electrochemists and electrophysicists, died in exile on 2 October at his farm in Versoix.

Edwin V. Bearer, 60, a member of the Agricultural Department, Rutgers University, was killed in an automobile accident on 16 October near Allentown, New Jersey, while traveling to address a group of high school students.

Carl R. McCrosky, 56, head of the Chemistry Department, Syracuse University, died on 16 October at the Madison, Wisconsin, General Hospital. Dr. McCrosky was returning to Syracuse University after spending the summer in Oregon.

Benjamin Clar, 62, retired physicist of the Bureau of Standards, died on 16 October in Washington, D. C., following a heart attack.

Gerald Francis Loughlin, 65, who had been associated with the U. S. Geological Survey for 39 years and chief geologist from 1935 until about two years ago, died unexpectedly on 22 October in Washington, D. C. He had spent the summer in research and work in New England.

H. Edmund Friesell, 72, dean of the University of Pittsburgh School of Dentistry since 1904, died on 10 October.

Joseph H. Gourley, 63, chief of the Department of Horticulture, Ohio Agricultural Experiment Station, Wooster, Ohio, and chairman of the Department of Horticulture and Forestry, The Ohio State University, died on 27 October following a week's illness.

In the Laboratory

Synthetic Media for Penicillin Production

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During a series of investigations by The Pennsylvania State College on the chemical purification of penicillin for the Office of Production Research and Development of the War Production Board, a chemical medium known or "synthetic" medium was developed by the laboratory for the production of penicillin. The advantages of such a medium are: (1) it contains less extraneous material, therefore simplifying the task of selection and purification, and (2) it more readily permits the specific effect of chemical adjuvants. Several media were developed for surface and submerged growth in shake flasks, stirred bottles, and tanks.

Minimum requirements for the formation of penicillin in the species of *Penicillium* studied were observed, irrespective of the method of culture used.

Minerals: P, S, Fe, K, Mg, and Zn were found essential, as had been reported previously by the Northern Regional Research Laboratory and others. In addition, Cu (about 1 ppm) was necessary for penicillin formation. Most cultures gave best results when the K/Na ratio was greater than 1.

Carbohydrate: Some source of sugar, starch, or other material was necessary for significant penicillin formation. No carbohydrate was found superior to lactose, which has been generally used in industrial production in combination with corn steep solids.

Organic acids: All of the successful synthetic media contained some organic acid. Most of the common amino acids, fatty acids, hydroxy acids, keto acids, dicarboxylic acids, and tri-carboxylic acids were studied. Acetic acid gave the best results, but mixtures of acetic and formic acid and lactic acids performed nearly as well.

Nitrogen source: Some amino or ammonium nitrogen was found essential. Too high a concentration of either type cut the yield of penicillin.

Hydrogen-ion concentration: The control of pH is especially important. It was found essential that the pH be kept between 6.5 and 8.2 during the period of penicillin formation.

SURFACE GROWTH

A synthetic medium was devised using NRRL culture 1259.B21, the first organism generally used. The

assisted by H. D. McAuliffe, D. D. Deane, W. E. Grundy, A. C. Richer.

mold was grown in 1.5-l., round milk bottles stoppered with cotton plugs, and incubated at 23–25° C. in a horizontal position. About 250 ml. of the following basal medium was used per bottle: 4.0 per cent lactose, 0.5 per cent glacial acetic acid, 0.5 per cent NH_4NO_3 , 0.1 per cent KH_2PO_4 , 0.5 per cent NaNO_3 , 0.025 per cent $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 0.02 per cent $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, 0.004 per cent $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$, and 0.0005 per cent $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$. The pH was adjusted to 6.1 before sterilization so that the final acidity was above pH 5.6. An equivalent amount of potassium acetate may be substituted for the acetic acid, doing away with the necessity of adding KOH.

Many trials with this medium have given an average broth assay of approximately 50 Oxford units of penicillin/ml. in 7–10 days. Assays were run by the agar cup-plate method, using *Staphylococcus aureus* according to the Food and Drug Administration procedure. The growth was somewhat slower than in corn steep medium. The addition of phenylacetic acid in concentration up to 0.4 per cent increased the broth assay to from 80 to 100 units/ml., while the addition of both 0.4 per cent phenylacetic acid and 0.1 per cent cysteine or cystine gave from 120 to 150 units.

In using this medium for experimental work, it is necessary to adjust the concentration of the acetate ion and sugar to keep the pH in the desired range. The chief difficulty with this or similar media for surface culture is that penicillin formation is easily influenced by slight changes in environment. The use of a different container or even a tight or loose cotton stopper in the same type of bottle may cause enough difference in the rate of sugar utilization to alter the pH.

SUBMERGED GROWTH

The synthetic medium developed for surface culture was adapted to submerged growth with minor modifications, using cultures X-1612 and NRRL 1951.B25 (1).

On this type of medium, certain stages of fermentation are discernible either in shake flasks or tanks: (1) The organic salt is attacked with the release of carbon dioxide to raise the pH; (2) the sugars are attacked, forming acids which lower the pH. This is the period in which penicillin is formed most rapidly; and (3) as the sugars become exhausted, the mold attacks the acids formed from the sugar, and the pH again rises.

It is extremely important that the pH be kept below 8.2 at the end of the first stage. One effective method is to reduce the initial concentration of acetate. Some free acid may also be added during fermentation.

The use of more buffer is likewise effective, but the adjustment of the concentration of organic acid has been most satisfactory.

During the second stage the pH must be above 6.5. Control is more difficult than in the first stage but can be obtained to some extent by adjusting the sugar concentration. Less sugar tends to raise the pH; more sugar, to lower it. As suggested above, the use of more buffer is also effective, and the direct addition of acid and alkali may be employed if necessary.

SHAKE FLASK CULTURE

The medium used for shake flask experiments must be adjusted according to the size of container, depth of medium, type of stopper, and rate of shaking. The following basal medium is satisfactory for 1-l., cotton-stoppered Erlenmeyer flasks containing from 100 to 150 ml. of medium, the shaker moving a distance of 2.75 inches at 90 r.p.m.: 3.0 per cent lactose, 0.6 per cent glacial acetic acid, 0.5 per cent glucose, 0.5 per cent NH_4NO_3 , 0.2 per cent KH_2PO_4 , .05 per cent $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 0.02 per cent $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, 0.002 per cent $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$, and 0.0005 per cent $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$. The pH is adjusted to 6.1 with KOH.

When culture X-1612 is used under proper conditions of aeration, this medium produces from 100 to 150 units/ml. of penicillin in 6-8 days. The addition of 0.04 per cent phenylacetamide or β -phenylethylamine increases the broth assay approximately 50 units/ml.

STIRRED BOTTLE AND TANK CULTURE

Much of the developmental work on synthetic media was carried out in 20-l., pyrex glass bottles mounted in a water bath and stirred with a 5-inch, straight-blade stirrer at speeds of 300-500 r.p.m. The air was introduced by means of 1/32-inch holes drilled in a small-diameter aluminum tube placed across the bottom of the bottle. Approximately 12 l. of medium was used per bottle. The rate of aeration was 1-1.5 l. of air/l. of medium/minute. Two per cent octadecanol in lard oil (Swift's Mellocrust) was used as an antifoam agent according to recommendations from the University of Wisconsin (3). Synthetic media are very sensitive to overaddition of antifoam and require only a fraction of that used with corn steep media. Doubling the amount of antifoam used in stirred bottle culture may cut the penicillin yield in half.

The results of several typical experiments using culture X-1612 in stirred bottles are shown in Table 1. Medium VIII was similar to the formula for shake flasks given above, with the following changes: 1.5 per cent lactose, 0.4 per cent glacial acetic acid, and

the addition of 0.35 per cent KNO_3 . Medium was the same as VIII in mineral and sugar content but sodium acetate was used equivalent to 0.6 per cent glacial acetic acid and no adjustment of pH necessary. In the last column of the table the results of the penicillin assay with *Bacillus subtilis* is compared with the standard assay using *Staph.* It is possible to substitute sodium acetate for the potassium acetate medium using culture X-1612, but with slightly lower over-all yields. Many of the other media studied gave much poorer results under these conditions.

TABLE 1
PENICILLIN PRODUCTION ON SYNTHETIC MEDIA IN STIRRED BOTTLES

No.	Medium	%	Time (hr.)	Assay (u./ml.)
21A	VIII		108	167
21B	" + phenylacetamide	.025	108	262
21C	" + phenylethylamine	.025	96	192
22A	" + phenylacetamide	.025	108	294
22B	" + " + leucine	.05	108	384
23A	" + " + "		96	304
23B	" + " + "	.025	96	364
23C	" + " + cystine	.025	108	351
26A	VIII		90	164
26C	XIII (sodium acetate)		90	165

Of the adjuvants listed here, both β -phenylethylamine and phenylacetamide increase the broth assay as well as the *subtilis/auress* ratio. The further addition of the amino acid l-leucine or cystine has at times given stimulating effects. At other times stimulation has occurred from the addition of l-glutamic acid, and it is probable that the effect depends on some unknown factor.

The media described are suitable for commercial production and have been used at several plants for short periods. The chief disadvantages are that growth is slower than in corn steep media, their use requires more careful adjustment of conditions to conditions of stirring, aeration, and container size. In most cases the yields are slightly lower than those of corn steep media, but this fact is offset by the greater ease of purification of the resulting product. For research on the production of various penicillins, these media are superior to the corn steep variety.

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Tests of Screening Effectiveness Against Insects

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During the war a new mesh of wire window-screening was introduced, and over 60,000,000 square feet have already been manufactured. This screening has 18 warp (length) wires and 14 filler (width) wires to the inch in place of the standard 16 warp and 16 filler wires to the inch, resulting in rectangular rather than square mesh openings. Employing the same machinery, an appreciable increase in output was attained by converting from the 16×16 to the 18×14 mesh, because the warp wires were fixed and the shuttle putting in the filler wires required only 14 instead of 16 strokes to the inch.

It was also thought that the 18×14 mesh gave better protection against insects while utilizing about the same quantity of wire per square foot of screening. Tests were therefore run to determine quantitatively the comparative effectiveness of the 18×14 and 16×16 mesh as well as of other mesh sizes of screening having both square and rectangular openings. The wire of all screening was of standard diameter (0.011 inches).

The test insects included the common housefly, *Musca domestica*; the common southern house mosquito, *Culex quinquefasciatus*; the malaria-transmitting mosquito, *Anopheles quadrimaculatus*; and the yellow-fever carrier, *Aedes aegypti*. Undersized *A. aegypti*, produced by overcrowding and underfeeding the larvae, were also tested. Outdoor tests were made to test effectiveness of some of the screening samples against small, light-attracted insects such as leaf hoppers, gnats, and tiny moths.

The adult insects were introduced into screened cages, 12×4×2 inches, which were placed in gauze-covered jars. After 48 hours the insects were gassed, and those inside and outside the screened cages counted.

M. domestica, *C. quinquefasciatus*, and *A. quadrimaculatus* were not able to penetrate any of the screening used in these tests. The per cent of both normal and undersized *A. aegypti* escaping from the screened cages is given in Table 1.

It is seen that there was no difference in passage of the normal-sized insects through the 18×14 or 16×16 mesh screening. Although there was an apparent difference between the 18×14 and 16×16 mesh in the tests of the undersized *A. aegypti*, this difference was directly in line with the actual rather than the nominal mesh size of the screening. For the mesh sizes used in these tests the percentage escaping ap-

pears to be related to the longest dimension of the individual mesh openings (the diagonal) rather than to the shape of the openings alone, and gives a smooth curve when plotted as a function of the length of the diagonal. This might be anticipated from the fact that a mosquito, being an animate object, would attempt to find the direction of greatest clearance, the diagonal, in passing through the mesh opening. While the diagonal of 18×14 mesh screening is 0.0023 inches longer than that of the 16×16 mesh screening, the difference is not considered great enough to be of practical significance in screening effectiveness.

TABLE 1

A. aegypti—Normal size			
Mesh (warp × filler wires/inch)		Length of diagonal of mesh opening (inches)	Per cent escaping
Nominal	Actual		
18 × 18	18 × 18.7	0.0616	0 ± 0
18 × 18	18 × 18.4	0.0622	3 ± 3
18 × 18	18 × 17.6	0.0639	5 ± 2
18 × 16	18 × 15.5	0.0697	13 ± 3
16 × 16	16 × 16.2	0.0723	14 ± 3
18 × 14	18 × 14.3	0.0739	14 ± 3
18 × 12	18 × 12.5	0.0822	41 ± 6
14 × 14	14 × 14.2	0.0847	55 ± 6
A. aegypti—Undersized			
18 × 18	18 × 18.7	0.0616	6 ± 2
18 × 14	18 × 14.6	0.0728	28 ± 6
18 × 14	18 × 14.4	0.0736	32 ± 8
16 × 16	16 × 15.0	0.0759	50 ± 6

Since only the female mosquito bites and transmits disease, it was of interest to determine how effective screening was against females and males. Of a sampling of approximately 1,500 *A. aegypti*, 35 per cent were females and 65 per cent males. Of all the females present, 14 ± 3 per cent penetrated the screening, while of all males present, 17 ± 4 per cent passed through the screening. The difference was not significant.

In order to determine the effectiveness of screening against the small, light-attracted insects prevalent during the summer months, large, screened cages 1½ × 1½ × 1½ feet were placed out of doors and a small electric light suspended in each. Under the light was placed a large sheet of sticky paper to capture the insects that penetrated the screening. It is noted that for insects of this size, as well as for the mosquitoes, the insect penetration appeared to be related to the length of the diagonal of the mesh openings. As has been found in actual practice, the 18×18 mesh screening gave much better protection against these insects than did the 16×16 mesh.

This work was carried on with the cooperation and financial assistance of the Insect Wire Screening Bureau. A more complete report of the work will be published elsewhere.

Letters to the Editor

An Experimental Compressed-Air Plant Sprayer

While investigating the commercial possibilities of hydroponics in Aruba, N. W. I., special circumstances made it necessary to develop better plant-spraying equipment for insect control. During the past year and a half a compressed-air spraying unit has therefore been developed. This technic is based upon the well-known, compressed-air, paint spray equipment.

Air under pressure may be supplied either by an air compressor or by cylinders of compressed air, depending upon the requirements of the garden unit. The average operating pressure used is 100 pounds per square inch, the range being between 90 and 125 pounds.

The insecticide container must be constructed with sufficient strength to operate at a maximum operating air pressure of 125 pounds per square inch. The body of the Aruba unit is an 18-inch piece of heavy steel pipe 8 inches in diameter. Heavy steel caps are welded to each end, making the entire length 26 inches, with a 5-gallon capacity. Two-inch threaded nipples are welded to the top of the cylinder to receive the brass filling plug, the brass plug containing the air, and the spray piping assembly. Rubber washers are inserted under these brass plugs to insure an airtight fit. Smaller threaded nipples are welded to the body of the container to receive the $\frac{1}{2}$ -inch drain valve and the pressure gauge. Castors are attached to a suitable framework, and a handle is provided to enable the operator to move the equipment readily.

All fittings are of $\frac{1}{4}$ -inch size except the drain valve, which is $\frac{1}{2}$ inch in size. All valves and external piping should be of steel construction for safety. A pressure-release valve is necessary to release the air pressure when refilling the unit which, for safety reasons, is attached to the filling plug.

The spray fluid pipe outlet contains a valve which shuts off the spray supply to the spray nozzle. A $\frac{1}{4}$ -inch copper connecting tube inside the unit reaches to within $\frac{1}{4}$ inch of the bottom of the container. The spray fluid is forced through this tube from the container.

The air-line intake supplies air to both the container and the spray nozzle. A valve may be used to regulate the air pressure into the container. A copper tube extension of the air line into the container may or may not be installed. For completely dispersible contacticides no agitation of the spray is necessary in the container. Agitation should be provided when less stable sprays are used. Operating experience indicated that when an agitation tube is used it should terminate some distance (at least 6-12 inches) from the fluid outlet. At least for stable contacticides, the air pressures direct to the spray gun and into the spray container are equal.

Another valve on the air line controls the air supply to the spray nozzle. Heavy-walled rubber tubing, usually $\frac{1}{2}$ -inch oxygen or paint hose, is used to convey the air

from the source to the container and from the container to the spray nozzle. A similar hose also conveys the spray fluid from the container to the spray nozzle. The two hoses to the spray nozzle are taped together to facilitate handling. Special adaptor nipples are used to connect the hose couplings to the container piping.

The spray nozzle is the important feature of the type of equipment. In fact, the operating principle of the usual paint spray gun is the chief reason why this type of sprayer is superior to the usual agricultural sprayer. Any type of paint spray gun, suitable for high-pressure operation, is satisfactory. A De Vilbiss, Type MBC, paint spray gun works well. The fluid and the air adjustment valves are set to provide a finely divided spray.

A diagram of the unit is available upon request to the writer.

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Projection of Meteor Trails on the Moon

In a recent issue of *Science* (1946, 104, 146) there appeared a letter from N. J. Giddings, of the Bureau of Plant Industry, Soils and Agricultural Engineering, Riverside, California, relative to a remarkable chance observation made by him regarding the moon on 17 June 1931. The phenomenon was also witnessed by Mrs. Giddings.

This letter is referred to in the October issue of *Sky and Telescope* in Dr. Marshall's column, "Astronomical Anecdotes," and the suggestion is made that meteorites striking the moon might produce a flash visible on the dark side which might be seen with the naked eye. It seems to me that a more probable explanation is the following:

According to Mr. Giddings' letter, the time of observation was approximately 7:40 P.M. (P.S.T.?). Allowing for some small error in timing, it is clear that the sun could not have been below his horizon for, say, more than 25 minutes. The sky, therefore, must have been quite bright in the west, the direction in which the moon was seen, Mr. Giddings having stated that it was "new." I take it that the probable age was three or four days, since it is at this time that the dark side is most prominent. Now, suppose that at this time several meteors were entering the earth's atmosphere. Unless these were very bright, it is not likely that they would be seen against the bright twilight sky. But, should their trails cross the dark surface of the moon, they would be visible for just that portion of their path which had the dark side as its background. Thus, Mr. Giddings would be confirmed in his statement that the flashes were "definitely within the limits of the moon's outline." It is to be noted further that these flashes "streaked across the moon." This is how a meteor trail would appear,

projected against the dark side; but a meteorite impact on the moon itself would certainly appear, if at all, as a momentary pinpoint of light. I think that Mr. Giddings had the rare fortune to see several meteor trails projected against the dark side of the young moon, and that such is the simple explanation of this phenomenon. It seems strange indeed that such an unusual observation should have been "courteously discounted" apparently without any thought whatever being given to the matter, and *Science* is to be congratulated in calling attention to these observations.

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Whole-Blood Cholinesterase Determinations in Some Hematologic Dyscrasias; Low Cholinesterase Values in the Leucoses

The asthenia and extreme pallor attending the acute malignant leucoblastoses (leucoses) are considered to be, as in the comparable case of shock (*O. St. med. J.*, 1943, 39, 907; 1944, 40, 130; 1945, 41, 1107), manifestations of profound cholinergic intoxication. Death is the culmination of this intoxication, which operates to produce an irreversible shock state characterized by the atopic-exudative syndrome of thrombocytopenic purpura. The last phase is usually not accounted for on the basis of myelophthisis or leucoblastic infiltration.

Whole-blood cholinesterase determinations have been made in 14 leukemic patients from military hospitals to determine a possible basis for the cholinergic state. The series included five cases of acute and two of subacute myeloblastosis, one of acute monoblastosis, one of acute lymphoblastosis, four of chronic leukemic myeloblastosis, and one of chronic lymphatic leukemia. The blood cholinesterase values in leucoses were compared with those obtained in 18 patients with nonleukemic hematologic conditions, the latter series incorporating three instances of macrocytic and three of hypochromic anemia, three of polycythemia vera, one of eosinophilia of undetermined origin, one of idiopathic hypoprothrombinemia, and seven of benign systemic lymphosis (infectious mononucleosis).

In 13 of the 14 cases of malignant leucoblastosis, the blood cholinesterase was lowered to a degree proportional to the acuity and clinical severity. The exceptional case was that of stationary chronic lymphatic leukemia.

In the nonleukotic series all cholinesterase values, with four exceptions, were within normal range. In the macrocytic anemias the values were low, confirming the observations of Sabine (*J. clin. Invest.*, 1940, 19, 833). In one case of polycythemia it was elevated.

In neither series did the blood cholinesterase values parallel the erythrocyte or leucocyte counts or the hemoglobin concentrations. A confirmation of the independent variability of these factors was obtained experimentally in one case. By massive infusion of human plasma as a source of cholinesterase, the level of the latter in the blood of a patient with subacute myelogenous leukemia was raised to normal value. During the period when

the rise was extant there was abatement of the pallor and the prostration, but erythrocyte and leucocyte counts remained stationary, rising only after discontinuance of plasma administration when the cholinesterase content of the blood began to fall to its preadministration level.

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A Simply Constructed Biophotometer

Through the efforts of the U. S. Government and the American Red Cross, food and medical supplies were transported to prisoners of war and civilian internees in Japan. At our camp in Zentsuji, Shikoku Island, Japan, a limited number of supplies were received, including vitamin concentrates of all types. The diet at this camp, as in the majority of the Japanese POW camps, was inadequate in all respects, and many officer prisoners of war were showing symptoms of various nutritional deficiency diseases. Among these were complaints of night blindness, beriberi, etc. In order to distribute equitably the limited quantity of vitamin supplements to those who needed them most, a biophotometer for measuring minimal visible light was constructed by use of apple crates for framing, and cardboard from the Red Cross parcels for the sides.

The instrument was so constructed that a panel could be put between a light source in the bottom of the instrument and the patient's eye at the other end. In various positions in the panel were letters "E," cut out of the cardboard panel. The first "E" was covered with 1 sheet of tissue paper, the second with 2 sheets, and so on until the twelfth "E" was covered with 12 sheets. Thus, the amount of light from the bulb reaching the patient's eye was graded. Across the other end, through which the patient looked at the panel, were stretched varying numbers of pieces (1 to 8) of blue cellophane.

The 8 sheets of cellophane were placed over the eye-piece, and the number of "E's" that the patient could see was recorded. Then a sheet was removed and the number of "E's" recorded, this number obviously being either the same as with the 8 sheets, or more. This procedure was repeated until the patient could see all "E's."

By performing this test on a number of seemingly normal individuals who were receiving, in addition, vitamin supplements, a normal curve could be obtained by plotting the numbers of letters seen, i.e. the minimal visible light, vs. the number of colored cellophane slides. It was found that the total numbers of letters that could be seen by the normals averaged about 97 over the 8 slides (mildly deficient cases of avitaminosis A, about 75 to 90; badly deficient cases, less than 75).

The curves recorded as described above are very similar to those reported in the literature and indicate that such a simple instrument was reliable and could well be used in a clinic with a very small construction cost.

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Book Reviews

Mathematical methods of statistics. Harald Cramér. Princeton, N. J.: Princeton Univ. Press, 1946. Pp. xvi + 575. (Illustrated.) \$6.00.

The modern development of statistics has brought with it the use of mathematical techniques which have in the past been confined to the repertory of professional mathematicians. Unfortunately for nonmathematicians, the theory of probability, which is essential as a background to statistics, involves the use of advanced measure and integration theory, and the concomitant general apparatus of the theory of functions of real variables. Cramér's book is doubly welcome in that it contains both a remarkably complete treatment of the mathematical background to statistics and a treatment of statistical methodology itself, a combination not previously available.

The book is divided into three parts. The first part is devoted almost wholly to measure and integration. The second part gives the basic knowledge of probability required for statistics. The author's general point of view makes this part a study of random variables; games, permutations, combinations, etc., so dear to the hearts of probability textbook writers, are omitted, except as implicit in the binomial distribution. The development is carried through the central limit theorem (on the approximation to normality of the sum of a large number of independent random variables) and the law of large numbers. The problem of measure in infinitely many dimensions is avoided; probably for this reason the concept of convergence with probability 1 is omitted, and the function theoretic significance of the concept of convergence in probability (convergence in measure) is not explained. The third part of the book, comprising somewhat less than half, is devoted to statistical inference, subdivided into sampling distributions, tests of significance, and the theory of estimation. Periodogram analysis and the related theoretical problems of random processes are not treated because of lack of space.

The text presupposes a knowledge of calculus and familiarity with limiting processes. The writing, although almost always mathematically rigorous, does not sacrifice space to rigor. It is frankly a mathematics text, however, in spite of the numerous statistical examples, and as such is not for casual reading by outsiders. The full bibliography simplifies more extended study.

Both probability and statistics have been completely revolutionized in the 20th Century. The first has been put on a firm mathematical foundation, as rigorous as any other branch of analysis; the second, basing itself on probability, has been enabled to develop the delicate and elaborate techniques which give it its present importance. The author has succeeded admirably in his stated purpose of writing an exposition of the two fields, in their interrelations, from the modern point of view.

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Synthetic Penicillin

(Continued from page 433.)

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